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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/210,952	12/15/98	FAINZILBER M	2314-147

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EXAMINER	
CLEMENS,K	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/210,952	Applicant(s) FAINZILBER ET AL.	
	Examiner Karen Clemens	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 1999 and 27 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-47* is/are pending in the application.

4a) Of the above claim(s) *5, 12, 15, 22, 24, 26-27, 29-31, 33-36 and 37-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/6/99* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *Notice to Compy w/ Seq. Rules* .

DETAILED ACTION

1. The Examiner of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Karen Clemens in Art Unit 1644, Technology Center 1600 ((703) 308-8365).

2. This application contains sequence disclosures in the specification and the claims that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached "Notice To Comply With Requirements For Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures."

Specifically the conopeptides recited in claims 27-36 require a specific SEQ ID NO adjacent the referenced sequences.

Applicant's must provide a substitute computer disk which includes the aforementioned peptide sequences, a substitute paper copy of the "Sequence Listing" as well as an amendment directing its entry into the specification and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e), 1.821(f), 1.821(g), 1.825(b) or 1.821(d). Applicant is reminded to amend the specification to account for any sequences with 4 or more amino acids.

3. Claims 1-10 and 12-47 are currently pending.

4. Applicant's election of Group I, claims 1-6, with traverse in Paper No. 11, dated 4/27/00, is acknowledged. However, upon reconsideration the restriction requirement has been modified as set forth below.

5. Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claims 1-10 and 12- 36, drawn to a substantially pure conopeptide, classified in Class 530, Subclass 300.

II. Claims 37-47, drawn to an isolated nucleic acid encoding a conopeptide, classified in Class 536, Subclass 23.5.

Groups I and II are different products. They differ in structure and modes of action and are therefore patentably distinct.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and because a search of any of these distinct inventions would not be co-extensive with a search of the others, restriction for examination purposes as indicated is proper.

7. Applicant is further required under 35 U.S.C. §121:

(I) to elect:

A) a *specific* conopeptide such as the PnVIIA, Tx6.4, Tx6.9, Tx6.6, Tx6.5, J010, Gm6.7, Mr6.1, Mr6.2 or Mr6.3 conopeptide recited in claims 27, 28, 29, 30, 31, 32, 33, 34, 35 or 36, respectively, if Group I is elected. These conopeptides differ in their physicochemical properties and are therefore patentably distinct.

B) a *specific* nucleic acid such as those encoding the propeptide/peptide of the conopeptides PnVIIA, Tx6.4, Tx6.9, J010, Tx6.6, Tx6.5, Gm6.7, Mr6.1, Mr6.2 or Mr6.3 conopeptide if Group II is elected. These nucleic acids differ in their physicochemical properties and are therefore patentably distinct.

(II) to list all Claims readable thereon including those subsequently added. Currently Claims 1-10 and 11-26 are generic.

8. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims

subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

9. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP 809.02(a).

10. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

11. During a telephone conversation with Stephen Saxe on 4/18/01 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10 and 12- 36 as it reads on the Tx6.4 conopeptide recited in claim 28. Affirmation of this election must be made by applicant in responding to this Office action.

12. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

13. Claims 1, 2, 4, 6, 7, 8, 10, 13, 14, 16, 17, 18, 19, 20, 21, 23, 25 and 28, as they read on the Tx6.4 species "Trp-Leu-γGlu-Cys-Ser-Val-Trp-Phe-Ser-His-Cys-Thr-Lys-Asp-Ser--γGlu-Cys-Cys-Ser-Asn-Ser-Cys-Asp-Gln-Thr-Tyr-Cys-Thr-Leu-Met-Hyp-Hyp-Asp-Trp" recited in claim 28 are under examination.

However, since the elected conopeptide Tx6.4 species recited in claim 28 is now found to be free of the prior art, the prior art search has been extended to include the J010 conopeptide species recited in claim 32, "Cys-Lys-Thr-Tyr-Ser-Lys-Tyr-Cys-γGlu-Ala-Asp-Ser-γGlu-Cys-Cys-Thr-γGlu-Gln-Cys-Val-Arg-Ser-Tyr-

Cys-Thr-Leu-Phe" wherein the C-terminus is amidated. Claims 1, 2, 3, 6, 7, 8, 9, 13, 20, 21 and 32 read on this species.

Claims 5, 12, 15, 22, 24, 26-27, 29-31 and 33-36 of Group I and claims 37-47 (Group II) are withdrawn from further consideration by the Examiner, 37 C.F.R. §1.142(b), as being drawn to non-elected inventions.

Claims 1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32 are currently under examination.

14. Papers filed on 13 October, 2000, in response to the Decision Refusing Status Under 37 CFR 1.47(a) mailed on 14 July, 2000, included the Declaration signed by the previously non-signing inventors in compliance with 37 CFR 1.63 rendering further reconsideration under 37 CFR 1.47(a) moot. However, the declaration signed by joint inventor Maren Watkins submitted with the petition filed on 29 July, 1999, is improperly signed by Brent K. Brown. Consequently, a new oath or declaration in compliance with 37 CFR§§ 1.63 signed by joint inventor Watkins must be submitted to the Office.

15. The disclosure is objected to because of the following informalities: On page 2, line13, the word "been", and on line 22 the word "membrane", are misspelled.

16. The filing date of claims with limitations which include the conopeptides of SEQ ID NO:1-15 is deemed to be the filing date of the instant application, filed 12/15/98, as no support for SEQ ID NO:1-15 is found in priority document, filed 12/16/97.

17. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

A. Claims 1-4, 6-10, 13-14, 16-20, 21, 23, and 25 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

There is no support in the specification or the claims as originally filed for the proviso "when all Xaa_{10} are des-Xaa_{10}, then both Xaa_9 are des-Xaa_9 or any amino acid" recited in lines 14-15 of claims 1 and 7. There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes new matter. Applicant is required to cancel the new matter in the response to this Office action. Alternatively, applicant is invited to provide sufficient written support for the limitations indicated above.

B. Claims 1-4, 6-10 and 13 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to the conopeptide of SEQ ID NO:**1** wherein Xaa_4 is γGlu, or each Xaa_1 is des-Xaa_1, or at least one Xaa_1 is any amino acid or Xaa_9 is des-Xaa_9 and Xaa_{10} is des-Xaa_{10}, or Xaa_9 is any amino acid; the conopeptide of SEQ ID NO:**2** wherein the Xaa_4 is γGlu, or each Xaa_1 is des-Xaa_1, or at least one Xaa_1 is any amino acid or Xaa_9 is des-Xaa_9 and Xaa_{10} is des-Xaa_{10}, or Xaa_9 is any amino acid; and the conopeptide of SEQ ID NO:**3** wherein Xaa_3 is γGlu. The claims are further drawn to the conopeptide of SEQ ID NO:**4** wherein Xaa_4 is γGlu; the conopeptide of SEQ ID NO:**5** wherein Xaa_5 is γGlu; and to SEQ ID NO:**6-15** wherein Xaa_1 is Trp or 6-bromo-Trp, Xaa_2 is γGlu or Glu, and Xaa_3 is Hyp or Pro.

However, Applicant's disclosure in limited to the specific conopeptides which include PnVIIa, Tx6.4, Tx6.9, Tx6.6 and Tx6.5 (SEQ ID NO:6-8, 10-11), wherein Xaa_1 is Trp, Xaa_2 is γGlu and Xaa_3 is Hyp and the C-terminus has a free carboxyl group; J010 (SEQ ID NO:9) wherein Xaa_2 is γGlu and the C-terminus is amidated; Gm6.7 and Mr6.1 (SEQ ID NO:12-13) wherein Xaa_1 is Trp, Xaa_2 is γGlu, and Xaa_3 is Hyp; and Mr6.2 and Mr6.3 (SEQ ID NO:14-15) wherein Xaa_1 is Trp, Xaa_2 is γGlu, and the C-terminus is amidated.

The claimed invention which is drawn to a genus of conopeptides may be adequately described if there is a sufficient description of a *representative number of species*. To satisfy the disclosure of a

"*representative number of species*" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary *common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.* The claimed genus may also be adequately described through disclosure of sufficient *relevant, identifying characteristics* to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. "*Relevant, identifying characteristics*" includes structure or other physical and/or chemical properties, functional characteristics *coupled* with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show that applicant was in possession of the claimed genus.

In the instant case, however, there is no described or art-recognized correlation or relationship between the *structure* of the instant invention, the conopeptides of SEQ ID NO:1-15 with the designated alternative amino acid residues, and it's *function* as an agonist of neuronal pacemaker cation channels, upon which the instant invention is based. Therefore one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of the aforementioned conopeptides in which the features essential to the instant invention are retained.

Consequently, the claimed invention is not described in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the invention. See *Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).* Applicant is also directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

C. Claims 1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for use of the specific conopeptides PnVIIA and TxVIIA as agonists of neuronal pacemaker cation channels does not reasonably provide enablement for use of the conopeptides of SEQ ID NO:**1** wherein Xaa_4 is γGlu, or each Xaa_1 is des-Xaa_1, or at least one Xaa_1 is any amino acid, or Xaa_9 is des-Xaa_9 and Xaa_{10} is des-Xaa_{10}, or Xaa_9 is any amino acid; or the conopeptide of SEQ ID NO:**2** wherein the Xaa_4 is γGlu, or each Xaa_1 is des-Xaa_1, or at least one Xaa_1 is any amino acid, or Xaa_9 is des-Xaa_9 and Xaa_{10} is des-Xaa_{10}, or Xaa_9 is any amino acid; or the conopeptide of SEQ ID NO:**3** wherein Xaa_3 is γGlu; or the conopeptide of SEQ ID NO:**4** wherein Xaa_4 is γGlu; or the

conopeptide of SEQ ID NO:**5** wherein Xaa_5 is γGlu; or the conopeptides of SEQ ID NO:**6-15** wherein Xaa_2 is γGlu or Glu, or Xaa_3 is Hyp or Pro, or wherein Xaa_1 is Trp or 6-bromo-Trp, or the conopeptides Tx6.4, Tx6.9, Tx6.6 and Tx6.5 (SEQ ID NO:6-8, 10-11), wherein Xaa_1 is Trp, Xaa_2 is γGlu and Xaa_3 is Hyp and the C-terminus has a free carboxyl group; J010 (SEQ ID NO:9) wherein Xaa_2 is γGlu and the C-terminus is amidated; Gm6.7 and Mr6.1 (SEQ ID NO:12-13) wherein Xaa_1 is Trp, Xaa_2 is γGlu, and Xaa_3 is Hyp; and Mr6.2 and Mr6.3 (SEQ ID NO:14-15) wherein Xaa_1 is Trp, Xaa_2 is γGlu, and the C-terminus is amidated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The specification discloses the affect of the PnVIIA and TxVIIA conotoxins on ion channel activity as well as the identity of the conotoxins Tx6.4, Tx6.9, Tx6.6, Tx6.5, J010, Gm6.7, Mr6.1, Mr6.2 and Mr6.3 as recited in claims 28-36, respectively.

However, the specification fails to provide *sufficient guidance* or a sufficient number of working examples in the use of the peptides of SEQ ID NO:1-15, each with variable amino acids, or the conotoxins Tx6.4, Tx6.9, Tx6.6, Tx6.5, J010, Gm6.7, Mr6.1, Mr6.2 and Mr6.3, as recited in claims 28-36 for use as agonists of neuronal pacemaker cation channels as disclosed. It is known to one skilled in the art that the disulfide framework of the conopeptides act as the backbone structure for the peptide, however slight species variation is the hypervariable loop regions can result in distinct pharmacological activities (see Shen et al., Drug Discovery Today (5):98-106, page 99, 2nd column in particular). It is not disclosed in the specification or known to one skilled in the art which amino acid changes can be made while retaining the ability of the conopeptides to function as an agonist of neuronal pacemaker cation channels. Predicting which amino acid changes can be made requires a knowledge of, and guidance with respect to, which amino acid alterations, if any, are tolerant of modification and a detailed knowledge of the ways in which the product's structure relates to its functional usefulness. Absent functional data on the γ-conopeptides, other than PnVIIA and TxVIIA, and absent data revealing the amino acids critical for the function of these peptides as agonists of neuronal pacemaker cation channels one of skill in the art would be unable to predict if the numerous other conopeptides encompassed by the claim will function similarly. To use the invention as disclosed would require of the skilled artisan undue experimentation, such as testing numerous peptides with multiple variations for use as an agonist of neuronal pacemaker cation channels.

In view of the lack of sufficient guidance in the specification and limited number of working examples, the unpredictability in the art and the breadth of the claims it would take an undue amount of experimentation for one skilled in the art to practice the invention as claimed.

18. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention."

Claims 1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 1, 7, 14, 16 and 18 are indefinite and ambiguous in the recitation of "***having*** the general formula" in line 2 of the instant claims. It is unclear if *having* is limited specifically to the recited peptide or if the recited peptide comprises a portion of a larger polypeptide. The Office interprets the term "having" as open-ended and, if intended to be open-ended, prefers the term "comprising", and if intended to be closed, prefers the term "consisting of".

Claims 20, 21, 23, 25, 28, and 32 are indefinite and ambiguous in the recitation of "Tx6.4" and "J010". The terms refer to both a generic as well as a specific peptide sequence and it is unclear which sequence the terms are to represent.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 3, 6- 9, 13, 20, 21 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. 5,432,155 (see IDS, PTO form 1449).

The '155 Patent teaches the J010 peptide "**C**KTYSKY**C** γGlu ADS γGlu **CC**T γGlu Q**C**VRSY**C**TLF" (SEQ ID NO:10 of 'the 155 Patent, see column 15, Example 10 in particular). The '155 teaches the amidation of the peptides to yield fully protected amide intermediates (see column 9, first paragraph in particular).

Therefore, the reference teachings thus anticipate the claimed invention.

20. Claims 1, 7 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Eldridge et al. (*J. Virology* 66:6563-6571).

Eldridge et al. teach the *ctl* peptide, "A**C**AETGAV**C**VHNDE**CC**SGA**C**SPIFNY**C**LPQ" a conotoxin-like peptide from Baculovirus (see page 6565, Figure 2 in particular).

Therefore, the reference teachings thus anticipate the claimed invention.

21. Claims 1-4, 6-10, 13-14, 16-20, 21, 23, 25, 28 and 32 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Clemens whose telephone number is (703) 308-8365. The examiner can normally be reached Monday through Friday from 8:00 AM to 5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Karen Clemens, Ph.D.
Patent Examiner
Technology Center 1600
April 20, 2001

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